International Journal of Research in Medical Sciences
Shah NA et al. Int J Res Med Sci. 2015 Sep;3(9):2156-2160
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20150596

Review Article

Counterfeit drugs in India: significance and impact on pharmacovigilance

Nehal A. Shah*, Bhagya M. Sattigeri, Nirav N. Patel, Haresh A. Desai

Department of Pharmacology, Sumandeep Vidyapeeth, S.B.K.S. MI&RC, Piparia-391760, Vadodara, Gujarat, India

Received: 17 July 2015
Accepted: 11 August 2015

***Correspondence:**
Dr. Nehal A Shah,
E-mail: nehalsbks@gmail.com

ABSTRACT

Counterfeit drugs have emerged as a major global problem. This issue has been brought to the centre of the Indian media due to the death of 15 women attending a sterilization camp in Chhattisgarh. India's pharmaceutical industry exports drugs worth 15 billion dollars, which means a high prevalence of counterfeiting in India's drug industry has global repercussions. However, accurate figures on the extent of counterfeit drugs in India are not available. The scientific literature as well as media reports often quotes figures of 10-35%, though studies done by the Indian Government dispute this. Counterfeit drug numbers have been known to be under represented by Governments due to fear of undermining their economy and health systems. On the other hand, rival companies in other countries may have an incentive to over hype India's counterfeit problem to dent India's growing status as the leading global supplier of generic medicines. Lack of clear definitions and differences between laws of countries further complicate reporting. A high prevalence of counterfeit drugs has a large impact on both health and economic indicators. Additionally, counterfeit drugs provide significant challenges to Pharmacovigilance programmes. Hence, here we discuss the significance of use of counterfeit drugs in India and challenges faced by Pharmacovigilance due to the extensive use of counterfeit drugs.

Keywords: Counterfeit drugs, Spurious drugs, Pharmacovigilance, Economic impact

INTRODUCTION

Counterfeit drugs have been described as a major problem around the world with major impact on global health and economies since the early 1980s. The issue was first addressed in 1985 at a conference in Nairobi. Since then, the problem of counterfeit drugs has unfortunately continued to grow with developing countries most affected. Currently the market for counterfeit drugs is estimated to be at US $200 billion. This represents more than 15% of the global pharmaceutical market. In developed countries the market share for counterfeit drugs is 1% of total drugs while in developing countries this number reaches 30%.[1,2] International reports suggest India to be the hub for counterfeit drugs. Death of 15 women attending a sterilization camp in Chhattisgarh recently has brought this issue to the forefront of the Indian media. India exports 15 billion dollars (1.5%) worth of drugs annually and is ranked 4th in the world in terms of production volumes. India exports its products to more than 200 countries and over 55% exports are to the highly regulated markets. In particular India exports generic medicines and is now the leading supplier of low-cost generic drugs to Africa and other developing countries.[2] Such countries may not have sufficient systems to test the quality of their drug imports. It becomes even more important for India to ensure the quality of their exported drugs. Hence, a high prevalence of counterfeit drugs in India has repercussions not just in India but globally. Here we discuss, concerns with varying definitions of counterfeit drugs, as well as its extent and impact on economic, health and Pharmacovigilance Programs.

Definition of counterfeit drugs

The definition of counterfeit drugs varies greatly between different countries. There is an absence of uniformly accepted definition for counterfeit drugs.[3]

According to Black's law dictionary counterfeit drugs are "drugs made by someone other than the genuine manufacturer, by copying or imitating an original product without authority or right, with a view to deceive or defraud, and then marketing the copied or forged drug as the original". [3]

The World Health Organization (WHO) defines counterfeit medicines as "A counterfeit medicine is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging."[3]

The United States definition by the Drug and Cosmetic Act is, "A drug which, or the containers or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor."[3]

The WHO categorizes counterfeit drugs into 6 categories based on type and prevalence:

1. No active ingredients (32.1%).
2. Incorrect amounts of active ingredients (20.2%).
3. Incorrect ingredients (21.4%).
4. Correct quantities of active ingredients but fake packaging (15.6%).
5. An original product that has been copied (1%).
6. High levels of impurities and contaminants (8.5%).[4]

India does not have an official definition for counterfeit drugs. Section 17-B of Drugs and Cosmetics Act, 1940 has defined spurious drugs (subsequently amended in 1980) as "A drug shall be deemed to be spurious if it is manufactured under a name which belongs to another drug, if it is an imitation of another drug or if it has been substituted wholly or partly by another drug or if it wrongly claims to be the product of another manufacturer."[4]

Spurious drugs have been divided into the following categories:

1. Category A (Spurious and Adulterated Drugs): This category includes formulations where the true identity is concealed and purposely made to resemble some brand drug with intent to deceive. There may or may not be presence of active ingredients. On most occasions the manufacture of such drugs is illegal and done by unlicensed manufacturers. Such products may be adulterated and contain harmful ingredients.

2. Category B (Grossly sub-standard drugs): Legally licensed companies manufacture such drugs. Such drugs may include vaccines failing potency tests or tablets failing disintegration tests or liquid preparations with microbial contamination.

3. Category C (Minor defects): Legally licensed companies manufacture such drugs which may have minor defects that do not cause any significant harm.[4]

There are several concerns with the WHO definition of counterfeit drugs. A major concern is that the WHO definition is too broad and may even affect the use of legitimate generic drugs. From an Indian perspective the most troubling part of the definition is the "false representation in relation to identity or source" and the fact that the drug would be declared fake if it ends up in a country where it is not registered. Concerns arise as differences in packaging may be due to batch to batch variation and not due to fraud. The definition as currently constituted regards such variations as counterfeit even if the drug has appropriate quality and constituents. Such ambiguity in the definition has led to problems in exports to South America via the European Union.[5]

While the Indian Government has fought efforts of the WHO to expand the counterfeit drug definition to include even genuine generic drugs the Indian definition of spurious drugs too lacks specificity. The Delhi High Court noted in a case of Bayer vs. Cipla that using the current definition of spurious drugs would mean that no generic drug would be approved.[6]

Extent of counterfeit drugs in India

There are major discrepancies between reported counterfeit rates of Indian drugs. Media reports as well as the scientific literature often state 10-25 % of Indian drugs are counterfeit. A WHO report is often quoted as stating that 35% of counterfeit drugs come from India. On the contrary the Indian government disputes this observation and according to the studies conducted by Central Drugs Standard Control Organization (CDSCO) 0.05% -0.3% of drugs made in India are found to be "spurious". The WHO has stated that the figure of 35% is not based on any study and is falsely attributed to the WHO.[4] Overall there is a lack of reliable quantitative data on the extent of counterfeit drugs in India. Here we

discuss the various reported literature as well as media reports of prevalence of counterfeit drugs in India.

In 2007, the WHO funded a study conducted by Delhi Pharmaceutical Trust (SEAR Pharm Forum) that analyzed 10743 samples from 234 pharmacies throughout India and found 0.3% samples to be spurious.[7]

A study was done by the ministry of Health and Family Welfare in 2009 with the Central Drugs Standard Control Organization (CDSCO) – "Report on Countrywide Survey for Spurious Drugs" to estimate the prevalence of spurious drugs in the Indian market. Over 24,780 samples were collected from 40000 pharmacies over a period of 7 months. Samples were solid oral dosage forms, belonging to 9 different therapeutic groups: multivitamins, anti-malarial, anti-tubercular drugs, steroids, cardiovascular drugs, anti-diabetics, anti-histamines, NSAIDs, and anti-microbial. Only 0.046 % (11 samples) was found to be spurious. Of the chemically analyzed samples (305 samples) 1% (3 samples) was found to be substandard.[8]

Another study focused on drugs such as chloroquine, ciprofloxacin, erythromycin, rifampicin, and isoniazid in pharmaceutical stores in Chennai and Delhi. In total 541 samples were collected from 52 pharmaceutical stores and subsequently subjected to 2 tests 1) semi-quantitative thin-layer chromatography and 2) disintegration testing. These tests measure amount of active ingredients in the samples. It was observed that 12% and 5% of the samples failed one or both tests at Delhi and Chennai respectively. The authors observed that the sample size was not large enough to make concrete conclusions and that the substandard quality of drugs may not be just due to counterfeiting. Their failures may have also been due to "substandard production, transport or storage".[9]

Odenlyl et al. (2003) investigated 8 brands of tablets containing sulfadoxine-pyrimethamine from different pharmacies in Nigeria to study their physicoequivalence and quality. Six out of the 8 brands were from India. The authors concluded with their observations that only 3 out of 8 brands passed the British Pharmacopoeia quality specifications and were physically and chemically found to be equivalent. Although this study did not distinguish between counterfeit and substandard drugs it shows the importance of reducing counterfeit drugs in our exports.[10]

In 2013 Ranbaxy USA (subsidiary of Indian pharmaceutical manufacturer Ranbaxy) was charged by the United States for issues relating to drug safety and fraudulence, suggesting certain drugs from factories in Himachal Pradesh and Madhya Pradesh were not up to the quality suggested by USFDA. Ranbaxy eventually settled the case for 500 million dollars. The drugs included generic acne drug Sotret , gabapentin and ciprofloxacin.[11] According to the Taxation and Customs Union (TAXUD) statistics released in 2005 75% of global cases of counterfeit drugs originate in India.[12] This demonstrates the need to raise standards of factories in India producing drugs to prevent misperceptions of counterfeit drugs coming from India.

A study showed that India was the country of origin of drugs seized in the European Union due to contravention of intellectual property rights in 31% cases.[13] However, often such seizures in the European Union have been found to be due to misinterpretation of international laws and definitions of counterfeit drugs. For instance, nearly 20 shipments of generic drugs from India that were enroute to Africa and Latin America were detained by the Dutch and German customs officials. They had operated with the false understanding that Intellectual Property (IP) status of in-transit drugs should be treated as if they were manufactured in the Netherlands. Seizures have also been initiated by some of the pharmaceutical companies like Du Pont & Merck, and Eli Lilly.[14]

Recently the US Trade Representative has placed India and 12 other countries on the 'Priority Watch List'. They allege 20% of drugs in the Indian market to be counterfeit drugs due to India's poor history of protecting Intellectual Property Rights (IPR).[15]

The 10-40 % figure that the media presents is mostly unverified and unsubstantiated as is the 35% WHO figure (later denied by the WHO.) Often these figures are used both by the media as well as the literature but this is done incorrectly.

There have been incidents where counterfeit drugs were clearly responsible for deaths of several patients. For instance, recently the death of thirteen women who attended a squalid sterilization camp in Chhattisgarh was linked to a batch of pills from a small drugs factory Mahawar Pharmaceuticals in Raipur. In 2012, about 300 infants died in Kashmir and the state's major pediatric hospital was blamed for the drugs supplied by them.[16]

Allegations of counterfeit production, poor protection of IPRs, the seizures by the European Union and the exaggerated counterfeit drug figures may be due to vested foreign interests looking to tarnish India's image as it becomes the world's leading generic drug supplier. On the other hand there have been clear incidents of counterfeit drugs leading to deaths of patients in India on several occasions. Often governments have been known to under represent their counterfeit figures due to fear of undermining their economy and health systems. In addition, studies may not have adequately distinguished between "substandard" drugs and counterfeit drugs. This proves there must be a thorough study conducted independent of vested interest to estimate the true prevalence of counterfeit drugs in India.

Effects of counterfeit drugs

Counterfeit drugs have a number of adverse effects on both health and economic aspects of a population. There

are various scenarios where counterfeit drugs can have adverse effects on health.

Scenario 1: The counterfeit drug contains no active ingredient and no harmful ingredients: In this case the patient does not get harmed directly by the counterfeit drug but indirectly through prolongation of sickness due to delayed treatment. Also antibiotic resistance may be wrongly diagnosed as a result of the ineffectiveness of the counterfeit drug.

Scenario 2: The counterfeit drug has no active ingredient but has harmful ingredients: Here, the patient may develop unexpected adverse drug reactions and cause harm to the patient by causing death or morbidity.

Scenario 3: The counterfeit drug has the wrong active ingredient: This scenario would be akin to the patient taking another drug instead of the prescribed without knowing it.

Scenario 4: The counterfeit drug has all necessary active ingredients and other ingredients but in the wrong quantities: This may lead to increased morbidity of the patient as well as an increased chance of antimicrobial resistance.[17]

High prevalence of counterfeit drugs would in addition cause a loss of confidence in health care system among the public.[17]

Economic effects of counterfeit drugs

Counterfeit drugs in turn cause economic burden by causing a subsequent increase in morbidity, adverse drug reactions and drug resistance. In addition to increased morbidity there is an increase mortality, which can also lead to loss of economic potential. Sale of counterfeit drugs will harm sale of genuine drugs hence, affecting companies that have invested in quality, research and development of drugs. This may also deter companies from investing in research and development as well as deter foreign investments. There is also a significant loss of tax revenue to the government. In addition to this large amounts must be spent to protect the supply chain of drugs and creation of systems that can detect counterfeit drugs. Counterfeit drugs can lead to the ban of Indian companies in other countries as described above along with an additional cost for fines.[17]

Counterfeit drugs and pharmacovigilance

Pharmacovigilance programs rely on spontaneous reporting of adverse drug reactions (ADRs) and subsequent causality analysis. These programs work under the assumption that the suspected drug formulation includes all correct ingredients in the doses as given on the label. A high prevalence of counterfeit drugs would alter causality analysis and inferences including incorrect attribution of ADRs to specific active ingredients. Care must be taken not to be "over vigilant" so that patients are not deprived of much needed medications. Pharmacovigilance programs must consider the possibility of counterfeit drugs in their assessments. Pharmacovigilance personnel in particular must keep counterfeit drugs in the back of their minds when coming across strange or unexpected adverse reactions. Questions must be asked regarding the source (internet, dealer, pharmacy, etc.) and if there is any doubt about the source then it must be mentioned in the report with reasons stated. However, it would be impossible to track every medication prescribed.[18]

CONCLUSION

Counterfeit drugs arising in India have created problems across the globe. Countries must come together to address the issue of counterfeit drugs and agree on a single definition. There is a need to conduct reliable unbiased studies on the prevalence of counterfeit drugs in India, which would help in improvement of the health care system.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Shah NA, Sattigeri BM, Patel NN, Desai HA. Counterfeit drugs in India: significance and impact on pharmacovigilance. Int J Res Med Sci 2015;3:2156-60.